

**DEVELOPING EBOLA & MARBURG VACCINES**

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There is currently no vaccine or antiviral therapy to prevent or treat infection with Ebola or Marburg virus. Attempts to vaccinate against Ebola and Marburg viruses using a variety of classical vaccine strategies have failed, and developing a live attenuated virus vaccine is considered too dangerous. However, it has been shown that a single-dose immunization with a recombinant vaccine that expresses Ebola virus proteins solidly protects monkeys against an otherwise deadly infection. These results were published in Nature in August 2003 (Ref: Nature 424 (6949):681-84 (2003)). Based on these results, Crucell decided to develop a vaccine against Ebola and Marburg.

Crucell entered into a Cooperative Research and Development Agreement (CRADA) with the Vaccine Research Center (VRC) of the National Institutes of Health (NIH) National Institute of Allergy and Infectious Diseases (NIAID) in the United States to jointly develop, test, and manufacture an adenovirus-based Ebola vaccine. (An adenovirus is a type of virus that causes little or no disease.) Under the terms of the agreement, Crucell has an option for exclusive worldwide commercialization rights to the Ebola vaccine resulting from this collaboration. The CRADA has been extended to cover vaccines against Marburg and Lassa infections.

In 2004, results of pre-clinical experiments, performed by the VRC and the US Army Medical Research Institute of Infectious Diseases (USAMRIID), showed that a single dose of Crucell's vaccine completely protected non-human primates against a very high Ebola virus challenge. Under a production contract with the NIH, Crucell is manufacturing the Ebola vaccine according to Good Manufacturing Practice (cGMP) requirements.

The Ebola vaccine is currently being tested for safety and potency in a Phase I clinical trial, which commenced in September 2006. Two groups of 16 volunteers have been enrolled and vaccinated. Clinical data is still blinded, however initial indications suggest that the vaccine is safe at the tested doses and appears to be immunogenic in a subset of subjects.

Crucell's Ebola vaccine is targeted toward government officials, military and healthcare personnel at risk, travelers, and people living in Ebola endemic areas in Africa. In addition, the vaccine could be used to provide protection from the lethal virus in the event of biological warfare.

In October 2008 Crucell announced that it received a National Institutes of Allergy and Infectious Diseases (NIAID)/National Institutes of Health (NIH) contract aimed at advancing the development of a multivalent filovirus vaccine that includes both Ebola and Marburg viruses. The contract provides funding of up to \$30 million, with additional options that may be triggered at the discretion of the NIH worth a further \$40 million.

## Ebola and Marburg Vaccine Production Process

Crucell's recombinant adenovirus-based Ebola vaccine is made by inserting selected parts of the Ebola virus into an adenoviral vector, which acts as a *vehicle* for vaccination delivery. The adenoviral vector carrying the Ebola material cannot replicate independently – it is 'replication incompetent'. Replication of the vector can only occur in PER.C6<sup>®</sup> cells. Once the vector carrying the Ebola material is inoculated into PER.C6<sup>®</sup> cells, large quantities of the vector are produced, making commercial-scale manufacturing of the vaccine possible. The resulting product then undergoes extensive purification before use as a vaccine.

This vaccination method provides a very important safety advantage, while ensuring that a strong immune response is elicited against the Ebola virus. The steps used in producing such a vaccine are outlined in a simplified form in the following diagram.

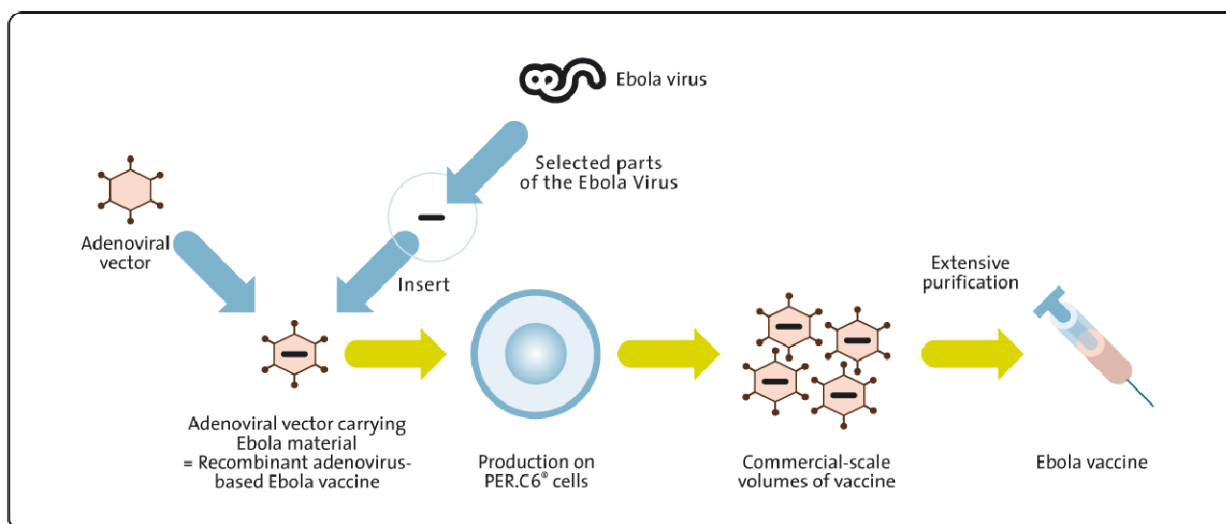


FIGURE 1. Ebola Vaccine Production Process

## About PER.C6<sup>®</sup> Technology

Crucell's PER.C6<sup>®</sup> technology is a cell line developed for the large-scale manufacture of biopharmaceutical products including vaccines. The production scale potential of the PER.C6<sup>®</sup> cell line has been demonstrated in an unprecedented successful bioreactor run of 20,000 liters. Compared to conventional production technologies, the strengths of the PER.C6<sup>®</sup> technology lie in its excellent safety profile, scalability and productivity under serum-free culture conditions. These characteristics, combined with its ability to support the growth of both human and animal viruses, make PER.C6<sup>®</sup> technology the biopharmaceutical production technology of choice for Crucell's current and potential pharmaceutical and biotechnology partners.